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THESIS DEFENSE

Cost Effectiveness of Azithromycin Versus Cefuroxime, with/without Erythromycin, in Hospitalized Patients with Community Acquired Pneumonia

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Key Words: Pneumonia, Azithromycin, Cefuroxime, Erythromycin,
Pharmacoconomics, Cost

There on


PURPOSE: To assess the cost-effectiveness of azithromycin monotherapy for hospitalized patients with community acquired pneumonia against the current practice of a second generation cephalosporin with/without erythromycin.

METHODS: A pharmacoeconomic analysis from the hospital perspective was performed on 266 evaluable patients from a multicenter clinical trial which was conducted from 1993-1995. No significant differences in clinical success or adverse events rates were detected. Health care resource utilization was extracted from the data base were transformed/converted to national costs. A sensitivity analysis was performed and statistics applied to the cost-effectiveness ratios

RESULTS: Of the 266 patients, 136 were randomized to azithromycin and 130 to cefuroxime \pm erythromycin. Clinical success rates were 78% for azithromycin, and 75% cefuroxime \pm erythromycin. The adverse event rate for the azithromycin group was 11.8%, and 20.7% for the control group. The antibiotic related length of stay was 5.8 days for azithromycin group, and 6.4 days for cefuroxime \pm erythromycin. Geometric mean treatment costs for the azithromycin group were \$4104 (95% CI, \$3874-\$4334) and the cefuroxime \pm erythromycin group were \$4578 (95% CI, \$4319-\$4837). The cost-effectiveness ratios were \$5265 for azithromycin, and \$6145 for cefuroxime \pm erythromycin ($P = 0.052$).

CONCLUSIONS: Despite a higher purchase price for azithromycin per dose, overall costs are less due to decreased resource utilization, administration costs, and hospital stay. Azithromycin has the advantage of once daily administration as well as a reduced overall length of stay. This results in azithromycin being cost-effective

when compared to cefuroxime \pm erythromycin for use in community acquired pneumonia which requires hospitalization.

(254 words, max of 250)

Despite an array of potent antimicrobials from which to choose, community-acquired pneumonia remains serious illness accounting for the sixth leading cause of death in the United States and the number one cause of death from infectious diseases.^{1,2} There are approximately four million cases of community-acquired pneumonia (CAP) annually, with 20% of these patients being hospitalized.¹ Among those hospitalized with CAP, mortality approaches 25%, especially if the patient requires admission to the intensive care unit.³⁻⁹

Initial therapy is necessarily empiric because clinical and radiographic findings are nonspecific and because of the difficulties in identifying an etiologic pathogen. In one-third to one-half of all cases, no pathogen is identified.¹⁰ In choosing initial therapy, many factors must be carefully considered, such as age, coexisting illness, smoking, severity of illness, and the patient setting prior to hospitalization. In 1993, the American Thoracic Society (ATS) published guidelines for the initial management of adults with CAP. These guidelines divide management into four severity categories, along with the suggested initial antimicrobial regimen.¹⁰

Cefuroxime is commonly employed as a typical second generation cephalosporin in categories 2 and 3 of the ATS guidelines. Cefuroxime is often used alone when atypical pathogens are not suspected. However, historically, a macrolide like erythromycin was frequently added when atypical pathogens were suspected for initial empiric coverage in hospitalized patients with community acquired pneumonia. Azithromycin is a new azolide agent that has a unique spectrum of activity similar to a combination of a second generation cephalosporin plus a macrolide, making it an appropriate single agent for empiric coverage in the

hospitalized patient with CAP. It's once daily administration, IV or PO, makes it less costly to administer than most conventional antimicrobials.

A pharmacoconomic analysis (compared to simple antibiotic price comparisons), provides a more accurate description of the true costs of treatment/healthcare.^{New 11}

Since pharmacoconomics is an outcomes-based science, determining an economic outcome requires a clinical outcome in conjunction.^{New 12} Conducting a prospective economic study involves all the resources and time necessary to conduct a clinical trial, and adds the specific requirements of an economic analysis. prospective economic analyses are seldom carried out. Therefore, to obtain rapid economic estimates without incurring the costs of the original clinical trial, modeling techniques have been widely utilized even though modeled data are inferior to actual cost accounting from clinical trials. Another approach is to capture the costs incurred from a completed clinical trial. This method requires few assumptions and can yield reliable results, depending upon the quality and depth of the data captured. Data available in patient case reports can be utilized to capture the majority of information necessary to conduct an economic analysis and include all major procedures, study drug regimens, treatment of adverse events, and length of stay.

When costs are assigned to each economic event, an analysis of the total costs of a hospitalized patient would result and can be compared in the aggregate with a sufficient sample size and have a meaningful purpose. Cost-effectiveness analysis (CEA) is an accepted method used for identifying, measuring, and comparing all the significant cost and consequences/outcomes of alternative health-care practices.¹² An integral part in evaluating the clinical usefulness of azithromycin monotherapy

regimen is to examine the effectiveness of the therapy and the resources required to administer the therapy.¹¹ Examination of the cost effectiveness is necessary in order have available the most appropriate empiric therapy by impacting formulary inclusion.

Review of the Clinical Trial

The clinical trial was a multicenter, parallel-group, randomized, open-label, comparative study of azithromycin versus cefuroxime in hospitalized patients with community acquired pneumonia caused by susceptible pathogens during 1993 to 1995.

Patients were randomized 1:1 to the azithromycin or control group. Patients in the azithromycin group received 500 mg IV qd, for 2-5 days, followed by 500 mg PO qd. Patients in the control group received cefuroxime 750 mg IV q8h, for 2-7 days, followed by 500 mg PO q12h, for a total of 7-10 days of therapy. For patients in the control group suspected of having atypical pathogens, (*Mycoplasma, Legionella or Chlamydia*) erythromycin 500-1000 mg IV q6h or 500 mg PO qd could be added at the discretion of the investigator, for up to 21 days.

Key inclusion criteria included adult inpatients with a new infiltrate on chest X-ray, and a clinical diagnosis of CAP which required treatment with IV antibiotics. Key exclusion criteria were major allergic reactions to macrolides or β -lactams, significant renal, hepatic, cardiovascular, or hematological disease, HIV infection, AIDS, metastatic tumor, septic shock, cystic fibrosis, mechanical ventilation, infection due to non-*hemophilus influenza* Gram-negative organisms, use of terfenadine, loratadine, or astemizole, and females who were pregnant or nursing.

Safety, clinical, microbiological, and radiographical assessments were performed and recorded during therapy, 10-14 post-therapy, and at long-term follow-up at 4-6 weeks. A description of the study population is shown in Table 1.

Adverse Events

All adverse were recorded and pursued. Abnormal laboratory test results that resulted in a change of study drug dosage was recorded as an adverse event. The reason for a patient discontinuing from the study was recorded.

Economic Methods

Because clinical outcomes are essentially equal, a cost-effectiveness analysis (CEA) is necessary to determine the most efficient means of differentiating between treatments. The primary cost of treatment in CAP is the hospital costs, therefore a Cost-Effectiveness Analysis from the institutional/hospital perspective was taken for this analysis.

The primary economic outcome measure is a two arm at the 10-14 day post-therapy follow-up period between azithromycin monotherapy versus control (cefuroxime with/without erythromycin as the comparative arm). Only patients with complete records were utilized. This analysis evaluated each treatment for community-acquired pneumonia, followed to the clinical outcome measure of success (cure or improvement) versus failure. This outcome measure is relevant and is useful from both clinical and economic standpoints.

The economic evaluation period began with the first day of treatment, which usually was the first day of hospitalization and terminated at the 4 to 6 week post-therapy follow up appointment. Additional length of stay attributing from adverse

events and treatment failures was included in the original length of stay unless re-hospitalization occurred. Re-hospitalization after the initial discharge is reported separately. The antibiotic related length of stay (LOS_{AR}) was determined for each patient in the initial hospitalization period. Where information on follow-up antibiotics/treatments, or where patients were not discharged from the hospital due to other illnesses, or hospital discharge date were not properly recorded in the case report forms, a blinded investigator was utilized to make a determination of additional treatments necessary, antibiotic related length of stay, or other necessary data where appropriate.

Early mortality was not included in the study. (n=1) An early death was defined as one that occurred before 72 hours after being randomized to treatment group.

Resource Utilization

The clinical trial database and case report forms were reviewed to determine all resources utilized. The information collected by the clinical investigators on the electronically maintained case report form contained complete information on each patient and included all dictation, summaries, labs, etc. The data for length of stay, procedures performed, medications, adverse events, clinical outcome, and other factors was extracted from the original data base and used to construct the pharmacoconomic data base. A partial listing of the procedures accounted for include all CAT scans; bronchoscopy; physical therapy; occupational therapy; X-rays; all lab procedures performed; thoracentesis; all concomitant medications, including those used to treat adverse events, and treatment failures; ventilation

perfusion scans; EKG's; ultra sounds; nebulizer treatments; IV site changes; heat and cold packs for phlebitis; incentive spirometry; cardiac echos; oxygen therapy; and telemetry.

Resource Costs

All utilized resources (medications/procedures) were measured in 1998 US Dollars. Costs were analyzed from three different levels/perspectives.^{New 2} Level I (drug budget perspective) covers study drug acquisition costs, only. Level II adds antibiotic related costs, such as preparation and administration, and additional medications used to manage adverse events and therapeutic failures. Level III adds the cost of hospitalization, and all other non-protocol driven resources utilized.

The average cost-to-charge ratio (70.46%) was applied to current charges for a medium sized hospital and then adjusted from our reference hospital's regional basis to the average national charges.^{New 12,13} Direct cost is defined as the cost of supplying the procedure/therapy to the average United States median sized community hospital.

The cost per bed day was determined by applying the weighted average time spent in each of 7 levels of care (n=2187 patients) for DRG 89 and DRG 90 (simple pneumonia with and without effusion) to the direct cost of supplying that care for a median sized reference hospital. That calculated cost per bed day was then adjusted from a regional cost to national cost by the percent change from our reference region to the national average cost for CAP.¹³ (Table 2) This cost included nursing administration time at each level of care and accounted, by means of the weighted

average, the cost and time spent in intensive care settings. This cost per bed day was applied to each day of hospitalization. Adverse events of concern to this analysis are those determined by the clinical investigator to be likely due to the study drug. The cost of all additional procedures/therapies incurred due to treatment modification from adverse events or treatment failure were accounted for according to their direct costs. The cost of study medications are included in table 4. We used our reference hospital's contract prices for all study medications. All non-study medications were assigned according to their direct RED BOOK¹⁴ cost. The future discounting of costs and/or outcomes was not necessary since the treatment of CAP does not extend beyond a one year time frame according to standard economic practices.

A standard decision tree (figure 1) analysis was utilized and costs for each treatment were calculated. The mean natural log costs for each treatment group was multiplied by the percent success or failure and then the exponent was taken to revert the log cost to a dollar amount. The costs for each pathway were calculated and are reported on the decision tree (figure 1).

The cost-effectiveness ratio (CER) was then calculated for each treatment arm by dividing the geometric mean cost of treatment by the probability of success for that regimen. The CER determines the cost per successfully treated patient and provide a meaningful measure of both costs and outcomes. The treatment arm with the lowest CER is considered to be the most cost-effective regimen, based on the assigned parameters.¹²

A sensitivity analysis was performed to see where differences in bed cost, antibiotic costs, or percent success rates would change the economic outcome. A

sensitivity analysis will test the strength of the economic model and its conclusions. The range of values in the sensitivity analysis accounted for variability in different clinical settings and over time. By varying these factors over a range, the sensitivity analysis allows for a more feasible extrapolation of the data to a variety of divergent clinical settings. The sensitivity analysis process shows the strength of the conclusions regarding cost-effectiveness. The sensitivity analysis included analyzing groups in three areas: success percentage; bed cost; and study drug costs. A sensitivity analysis will allow for differences in bed costs, contract prices of medications, price escalation over time, and different percentage success rates for unique hospital populations by varying the cost/rate for these items. Bed cost will be varied from \$200 to \$1200 per day. Cost of study medications will be varied by □ 50%. Success rate will be varied to the threshold limit, the point of equal cost effectiveness.

Statistical Analysis

Since clinical outcomes were equal, we used the geometric mean cost per patient and compared with a 95% confidence interval. We utilized a geometric mean cost, which is the most appropriate measure of central tendency for log normal distribution of data.

Patient baseline demographics were compared by χ^2 analysis or fisher's Exact test for categorical values, and two-way analysis of variance (ANOVA) was applied to continuous variables. Between-treatment comparisons of Levels III costs were made using a 95% confidence interval and Kruskal-Wallis one-way analysis of

variance test. Differences in clinical response rates between groups were analyzed by χ^2 analysis. All statistical tests of significance were two-sided, with a probability of a type-1 error of 0.05 to determine statistical significance. The statistical analysis was performed with SYSTAT Software 7.0,(SYSTAT, Evanston, IL).

Due to the unitless nature of the CER, statistical comparison of CERs is difficult. To construct valid statistics on differences in CERs between treatment groups, the parameters of clinical response rate, overall costs and resultant CERs were modeled iteratively utilizing the ADAPT II program.¹⁷ Adjustments for the log-normal distribution of costs, within clinical outcomes, were made for this modeling. A P value was calculated between treatment groups utilizing the standard error to facilitate comparisons.

Bias

For this analysis, an agreement was made between Pfizer, Inc. and the researchers, allowing the reporting of study results, favorable or not, and permitting unlimited access to all relevant data. The design was left to the judgment of the researchers. The comparative group is clinically relevant and complies with established guidelines for the treatment of community-acquired pneumonia.¹⁰ All assumptions were conservative in nature, specified, and justified with appropriate sensitivity analysis.

Results

Data from the case report forms for 266 patients were available for economic analysis. One patient from each group was not included in the economic analysis.

One case was an early death, and the other case was a protocol violation (partial gastrectomy/interference with oral absorption) which was not detected until the follow-up period. There were 136 economically evaluable patients in the azithromycin group and 130 patients in the control group, with 64 patients in the erythromycin subgroup. Baseline characteristics/demographics, and illness of each group are presented in Table 3. There were no statistically significant differences noted in the baseline characteristics/demographics between the two groups.

Clinical cure rates for the two groups at the 4-6 weeks post-therapy analysis were similar to the 10-12 day post-therapy time point. Thus the majority of patients remained cured at follow-up. No statistically significant difference ($p=0.465$) was observed between the two treatment groups in terms of clinical outcome at 4 to 6 weeks post-therapy, or the 10-14 day post-therapy ($p=0.42$).

Geometric mean LOS_{AR} data are shown on the decision tree in figure 1. Results from all three levels of costs from the two main groups are shown in table 5, and the azithromycin group and two subgroups are depicted graphically in figure 2. Results of the level III economic analysis are depicted also on the decision tree in figure 1. The decision tree combines the probabilities of success or failure in the actual clinical trial with the cost of each treatment arm. The results listed by each treatment arm show the resulting geometric mean cost (US \$) and LOS_{AR} for each possible outcome. As expected, for each treatment option, successful treatment resulted in a shorter length of stay than did clinical failure, and a lower mean cost. The level III costs demonstrates statistically significance difference with slightly overlapping 95% confidence intervals level between the azithromycin group and control group.

Additionally, when using Kruskal-Wallis one way analysis of variance a statistically significant difference was noted ($p=0.059$). The cost-effectiveness ratios were \$5265 per successfully treated patient with azithromycin and \$6145 per successfully treated patient with cefuroxime \pm erythromycin, ($P = 0.052$). The CER demonstrates a savings per successfully treated patient for the azithromycin group of \$880. Since the success rate was greater for the least costly treatment, an incremental cost analysis is not necessary to determine the increment of cost necessary to achieve a greater cure rate.

We examined two secondary outcome measures. One was the analysis of subgroups. We separated the control arm into monotherapy (cefuroxime) and combination therapy (cefuroxime with erythromycin) and then, compare baseline demographics and costs to azithromycin monotherapy.

The other secondary analysis was to analyze the late costs which incurred between the 10-14 day follow-up visit and the 4-6 week follow-up assessment. This included cost of hospital re-admissions and follow-up care and in-patient treatments identified from the CRF. The late costs were \$669 per patient (91 total hospital days in 9 patients) for the azithromycin group and \$92 per patient (12 total hospital days in 2 patients) for the control group, all of which occurred in the cefuroxime subgroup.

Subgroup analysis

When comparing the azithromycin group to either the cefuroxime subgroup, or the cefuroxime + erythromycin subgroup, there were no statistically significant

differences noted in the baseline characteristics/demographics between the two groups. As in the main group analysis, we have overlapping confidence intervals of the geometric mean costs at the 95% confidence level, between the azithromycin group (\$4104, 95% CI \$3874-\$4334) and the cefuroxime subgroup (\$4451, 95% CI \$4101-\$4800, $p > 0.05$). Between the azithromycin group and the cefuroxime + erythromycin subgroup (\$4713, 95% CI \$4329-\$5097), we overlap the 95% confidence intervals only by \$5, giving us a $P = 0.051$. The CER between the azithromycin group and the cefuroxime subgroup does not reach statistical significance, $P = 0.36$. The CER between the azithromycin group and the cefuroxime + erythromycin subgroup reaches statistical significance at $P = 0.037$. The mean cost savings achieved when using azithromycin over the cefuroxime is \$501 per successfully treated patient and \$1307 when using azithromycin in place of combination therapy of cefuroxime + erythromycin.

Adverse events

Adverse events with economic consequences were identified and include 16/136 (11.8%) in the azithromycin group, and 28/130 (21.5%) in the control arm with 5/66 (7.6%) in cefuroxime only subgroup, and 23/64 (35.9%) in the subgroup where erythromycin was combined with cefuroxime. These figures are slightly lower from the clinical results in that not all adverse events had a corresponding cost.

Results of sensitivity Analysis

Study drug-acquisition costs were varied by $\pm 50\%$, but the overall economic decision did not change. The cost for using azithromycin was consistently lower

than using cefuroxime \pm erythromycin. Hospital bed day cost varies from region of the country and by hospital size. Therefore, testing the cost per bed day over a wide range will account for this variance. The daily cost per hospital bed was varied from \$200-1200 per day. This range of daily bed costs did not change the economic outcome of this analysis from the point estimate cost per bed day used in this analysis of \$510.00.

Varying the rate of success can be useful to determine over what range of success the study drugs are cost effective or where the cost advantage exists for the control group. Results obtained by varying the clinical rate of success for each drug, independently, over a range of values from 50% to 95% is depicted in figure 3. The point of intersection of the two lines on the graph is the breakpoint where the cost-effectiveness changes. At this breakpoint, if azithromycin was 65% successful and the control group was 80% successful, the two groups would be equally cost-effective. Azithromycin remains cost-effective in the area to the right of the breakpoint. Overall, cefuroxime \pm erythromycin would have to be $>15\%$ more clinically effective than azithromycin to be more cost-effective.

Discussion

The mean total treatment cost per patient was \$474 less per patient in the azithromycin group than the control group and \$501 per successfully treated patient (CER) $P = 0.052$. This difference is not only statistically significant but economically important as well. Azithromycin demonstrated consistent lower utilization of resources on all three perspectives of costs. Level I costs include only

study drug purchase prices, Level II costs include the preparation and administration costs and subsequent treatment costs for treatment failures and adverse events. Level III costs expands level II costs and includes all costs to treat community acquired pneumonia, including the cost for hospitalization. The two treatment regimens are equal in efficacy, however, azithromycin demonstrated cost-effectiveness over either cefuroxime alone or combined with erythromycin. Azithromycin monotherapy demonstrated a slightly higher adverse events rate than cefuroxime alone but a lower rate than the combination of cefuroxime plus erythromycin. The re-hospitalization days were skewed in favor of the cefuroxime group with only 2 patients requiring additional hospital days (12 days), while 9 patients in the azithromycin group required 91 additional hospital days.

The sensitivity analysis demonstrated the robustness of the decision model used in this economic analysis. Varying the cost of the study drugs by \pm 50% or the cost of the hospital bed from \$200-\$1200 per day did not change this analysis. With the use of the sensitivity analysis in varying the percentage of success clinical patients, it was demonstrated that cefuroxime \pm erythromycin would have to have a clinical success rate greater than 15% better than azithromycin to be more cost-effective.

The majority of adverse events throughout the study were IV site problems, and digestive system problems like nausea, vomiting, diarrhea, and constipation. The three study arms experienced similar adverse events at different rates. The azithromycin group's rate of adverse events was in between the cefuroxime group,

with the lowest rate, and the cefuroxime + erythromycin group with the highest rate.

When the azithromycin arm was compared to the entire control arm, similar rates of adverse events was observed.

Summary

Even though azithromycin costs more per dose or day, it is dosed fewer times per day and thus has an inherent lower pharmacy admixture and administrative cost. In addition, in the overall analysis, there was approximately a $\frac{1}{2}$ day decrease in length of stay when compared to the control group. So despite the higher initial purchase price per dose, azithromycin has a decreased length of stay and decreased administrative costs which translates into an overall cost savings when using azithromycin as initial empiric therapy for community acquired pneumonia.

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References

1. Garibaldi RA. Epidemiology of community-acquired respiratory tract infections in adults: incidence, etiology, and impact. *Am J Med.* 1985;78:32S-37S
2. U.S. Department of Commerce, Bureau of the Census. *Statistical Abstract of the United States.* 104th Ed. Washington DC:USGPO, 1984
3. Bates JH, et al. Microbial etiology of acute pneumonia in hospitalized patients. *Chest.* 1992;101:1005-12
4. Fang GD, et al. New and emerging etiologies for community-acquired pneumonia with implication for therapy: a prospective multicenter study of 359 cases. *Medicine.* 1990;69:307-16
5. Marie TJ, et al. Community-acquired pneumonia requiring hospitalization: a five year prospective study. *Rev Infect Dis.* 1989;11:586-99
6. Woodhead MA, et al. Prospective study of the aetiology and outcome of pneumonia in the community. *Lancet.* 1987;1:671-4
7. Ortqvist A, et al. Severe community-acquired pneumonia: factors influencing need of intensive care treatment and prognosis. *Scand J Inf Dis.* 1985;17:377-86

8. Torres A, et al. Severe community-acquired pneumonia: epidemiology and prognostic factors. *Am Rev Respir Dis.* 1991;144:312-8
9. Pachon J, et al. Severe community-acquired pneumonia: etiology, prognosis, and treatment. *Am Rev Respir Dis.* 1990;142:369-73
10. Niederman, MS, et al. American Thoracic Society. Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. *Am Rev Respir Dis.* 1993;148:1418-1426
- New 11. Dickson, M, Bootman JL. Pharmacoconomics: an international perspective. In: Bootman JL, Townsend RJ, McGhan WF, eds. *Principles of Pharmacoconomics* Second Edition. Cincinnati: Harvey Whitney Books Co., 1996: Chapter 2. Pp.20-42
- New 12. Paladino JA, Fell RE. Pharmacoconomics analysis of cefmenoxime dual individualization in the treatment of nosocomial pneumonia. *Ann Pharmacother* 1994;28:384-389.
11. Detsky AS, et al. A clinician's guide to cost-effectiveness analysis. *American College of Physicians.* 1990;147-154
12. Bootman JL, et al. *Principles of Pharmacoconomics*, 2nd Ed. 1996, Harvey Whitney Books Company, Cincinnati, OH.

13. The American Hospital Association. The American Hospital Association Statistics. Chicago, 1995
14. Drug Topics [®]RED BOOK [®], Medical Economics Company, Montvale NJ, 07645, 1997
15. Tanner DJ. Cost containment of reconstituted parenteral antibiotics: personnel and supply costs associated with preparation, dispensing, and administration. *Rev Infect Dis* 1984;6(suppl 4):S924-37. (indexed to 1997 costs)
16. Hatoum HT. Microcost analysis of inpatient dispensing and administration of oral solids. *Am J Hosp Pharm* 1990;47:800-5. (indexed to 1997 costs)
17. D'argenio DZ, Schumitzky A. ADAPT II User's Guide (release 4). Los Angeles, CA: Biomedical Simulations Resource, University of Southern California, 1997

Table 1
CHARACTERISTICS

	Azithromycin	Comparative
Patients randomized	206	207
Received treatment	202	201
Assessed for clinical efficacy		
Evaluable:		
10-14 day visit	137	131
4-6 weeks	130	122
Assessed for safety	202	201
<hr/>		
Clinical Outcome	n (%)	n (%)
<u>10-14 days post therapy</u>		
Cure or improved	106 (77.4)	97 (74.1)
Failure	31 (22.6)	34 (26.0)
<u>4-6 weeks post therapy</u>		
Cure	98 (75.4)	87 (71.3)
Failure	32 (24.6)	35 (28.7)

The clinical outcomes were not significantly different per Chi-square analysis (p = 0.52)

Table 3
DEMOGRAPHICS

	Azithromycin n = 136	Control n = 130
Male (%)	58	62
Male, weight (kg) (mean, SD)	78.9, 20.1	80.4, 22.4
Female, weight (kg) (mean, SD)	73.1, 17.2	71.3, 17.9
Age, mean, SD, (range) (years) (18-93)	60.5, 17.6, (19-93)	60.1, 17.7
White (%)	75.3	75.9
Black (%)	21.3	22
Asian (%)	0.7	0
Other race (%)	2.7	2.1
Signs and symptoms at baseline		
Cough with sputum production (%)	86	87
Rales (%)	61	64
Fever (%)	58	58
Abnormal respiratory rate (%)	49	54
Rhonchi (%)	47	45
Other (%)	43	43
Concurrent disease syndromes at baseline		
Tobacco use	34	32
Hypertension	34	38
COPD (%)	32	37
Past history of pneumonia	22	22
Diabetes mellitus (%)	19	20
Emphysema	12	6
Asthma	10	10

The baseline demographics between groups were not significantly different.

Table 2 Calculations for cost per bed day

Table 4**Cost of study Medications/procedures utilized**

<u>Drug costs</u>	Per dose	Per day
Azithromycin 500 mg IV	18.00	18.00
Azithromycin 500 mg PO	10.00	10.00
Cefuroxime 750 mg IV	3.50	10.50
Cefuroxime 500 mg PO	4.75	9.50
Erythromycin 500 mg IV	1.75	7.00
Erythromycin 500 mg PO	0.15	0.60
<u>Antibiotic-associated costs</u>		
Preparation & administration	7.75 per IV dose ¹⁵	
	1.50 per PO dose ¹⁶	

Table 5 Level I, II and III costs in US dollars for patients treated with azithromycin or control.

Table 1

Calculations for cost per bed day						
Intensity of care	Intensity 1	Intensity 2	Intensity 3	Intensity 4	Intensity 5	Intensity 6 Intensity 7
Room related direct (fixed and variable supplies) (\$)	26	26	26	123	123	123
Indirect (depreciation)(\$)	33	33	33	126	126	126
Direct salaries (\$)	141	169	196	225	593	801
Indirect salaries (\$)	132	159	186	212	420	568
Total cost per bed day per intensity of care provided (sum)	332	387	441	496	1262	1618

Intensity of care	Intensity 1	Intensity 2	Intensity 3	Intensity 4	Intensity 5	Intensity 6 Intensity 7
% of time*	3.09	36.81	36.94	13.93	7.03	1.76
% of time times cost per bed day (\$)	10	142	163	70	89	28

Calculated national average cost per bed day for CAP \$510.00

* Percentage of time spent in each intensity of care for CAP (DRG 89 & 90) 1996 data

Table 2

DEMOGRAPHICS

	Azithromycin n = 136	Control n = 130	Cefuroxime Subgroup n = 66	Cef + Eryth Subgroup n = 64
Male (%)	58	61	61	61
Weight (kg) (mean, SD)	76.9, 18.2	76.4, 20.0	74.3, 21.5	78.6, 18.3
Age, years (mean, SD)	60.5, 17.6	60.1, 17.7	63.4, 16.5	56.4, 18.2
Caucasian (%)	75.3	76.9	77.3	76.6
Black (%)	21.3	20.8	19.7	21.9
Asian (%)	0.7	0	0	0
Other race (%)	2.7	2.3	3.2	1.5
Signs and symptoms at baseline				
Cough with sputum production (%)	86	87	x	x
Rales (%)	61	64	x	x
Fever (%)	58	58	x	x
Abnormal respiratory rate (%)	49	54	x	x
Rhonchi (%)	47	45	x	x
Other (%)	43	43	x	x
Concurrent disease syndromes at baseline				
Tobacco use (%)	34	32	x	x
Hypertension (%)	34	38	x	x
COPD (%)	32	37	x	x
Past history of pneumonia (%)	22	22	x	x
Diabetes mellitus (%)	19	20	x	x
Emphysema (%)	12	6	x	x
CHF (%)	11	13	x	x
Asthma (%)	10	10	x	x

SD = Standard deviation, kg = kilogram

COPD = Chronic obstructive pulmonary disease

The baseline demographics between groups were not significantly different. P > 0.05

Table 3**TREATMENT OUTCOMES**

Clinical Outcome	Azithromycin n (%)	Control n (%)	P
10-14 days post-therapy			
Cure/improved	106 (78)	97 (75)	0.54
Failure	30 (22)	33 (25)	
4-6 weeks post-therapy			
Cure	98 (75)	87 (71)	0.46
Failure	32 (25)	35 (29)	

Table 4

Level I, II and III costs in US dollars for patients treated with azithromycin or control

		Level I	Level II	Level III	% Success	CER*
<u>Azithromycin</u> (n=136)	Geometric Mean	\$113	\$231	\$4104	78.0	\$5265
	95% Confidence Interval					(\$3874-\$4334)
<u>(Control) Cefuroxime ± erythromycin</u> (n=130)	Geometric Mean	\$110	\$339	\$4578	74.5	\$6145
	95% Confidence Interval					(\$4319-\$4837)
						<i>P</i> =0.052

* CER = Cost-effectiveness Ratio

Figure Legends:

Figure 1: CAP: Decision Tree

CAP = Community-acquired pneumonia, () = Probability of success or failure, n =Number of subjects, \$ =Geometric mean cost per patient (1998 US \$), Days =geometric mean length of stay, \square = Choice node, \circ = Chance node, Success = Clinical cure + clinical improvement Failure = Clinical failure, Analysis (Level III Costs)

Figure 2: Levels of Cost

Figure 3: Sensitivity Analysis on the Probability of Success





